TARGETED MUTATION OF NEUROPEPTIDES REGULATING REPRODUCTION IN THE MOUSE, L. Muglia, C. Luedke, K-H. Jeong, L. Jacobson and J.A. Majzoub, Division of Endocrinology, Children's Hospital, Boston, MA 02115.

Inactivation of neuropeptide expression by homologous recombination in embryonic stem cells and subsequent production of homozygous deficient mice is a powerful tool for evaluation of in vivo gene function. We have exploited this methodology to assess the roles of corticotropin-releasing hormone (CRH) and oxytocin (OT) in modulation of mammalian reproduction. Previous studies by several groups employing foot shock, restraint, and food deprivation stress paradigms in combination with CRH antagonists have implicated CRH in the stress induced suppression of luteinizing hormone (LH) production. We have utilized CRH deficient mice to further evaluate the role of CRH during reproduction. CRH deficient mice exhibit impaired glucocorticoid production secondary to inadequate ACTH release during stressful and circadian stimuli, as well as low basal glucocorticoid production. Male and female CRH deficient mice are fertile despite adrenal insufficiency, indicating CRH is not required for reproduction. CRH deficient female mice, however, do not lactate normally and offspring fail to grow after the 2-3 days of life. Our recent studies have employed restraint stress, food deprivation, and adrenalectomy to elevate endogenous CRH in normal mice while evaluating differences in CRH deficient mice. Results of studies in male CRH deficient and wild type mice, with evaluation of LH, testosterone, mating efficiency, and fertility, will be presented. Additionally, we have made substantial progress in the production of an oxytocin deficient mouse line. The mouse oxytocin gene isolated from a 129/Sv genomic library was used to generate a null oxytocin vector for gene targeting. This construct encompassed 7.5 kb of oxytocin flanking sequences, while deleting the entire oxytocin coding region. The endogenous oxytocin allele has been efficiently targeted with this vector, with 10% of embryonic stem cell clones having undergone homologous recombination. High level male chimeras have been produced from several of these clones, and are currently being tested for germline transmission. This model will be used to explore the role of OT in sexual and maternal behavior, parturition, and fertility.

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